Site of Arterial Occlusion Identified by Transcranial Doppler Predicts the Response to Intravenous Thrombolysis for Stroke

EXHIBIT 3

tabbles.

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Background and Purpose—The objective of this study was to examine clinical outcomes and recanalization rates in a multicenter cohort of stroke patients receiving intravenous tissue plasminogen activator by site of occlusion localized with bedside transcranial Doppler. Angiographic studies with intraarterial thrombolysis suggest more proximal occlusions carry greater thrombus burden and benefit less from local therapy.

Methods—Using validated transcranial Doppler criteria for specific arterial occlusion (Thrombolysis in Brain Ischemia flow grades), we compared the rate of dramatic recovery (National Institutes of Health Stroke Scale score ≤2 at 24 hours) and favorable outcomes at 3 months (modified Rankin Scale ≤1) for each occlusion site. We determined the likelihood of recanalization at various occlusion sites and its predictors. Then, stepwise logistic regression was used to determine predictors of complete recanalization.

Results—Three hundred thirty-five patients had a mean age 69±13 years and 48.5% were women (median baseline National Institutes of Health Stroke Scale score 16 [range, 3 to 32], mean time to transcranial Doppler 140±84 minutes, and mean time to intravenous tissue plasminogen activator 145±68 minutes). Distal middle cerebral artery occlusion had an OR of 2 for complete recanalization (50 of 113 [44.2%], 95% CI: 1.1 to 3.1, $P=0.005$), proximal middle cerebral artery 0.7 (49 of 163 [30%], 95% CI: 0.4 to 1.1, $P=0.13$), terminal internal carotid artery 0.1 (one of 17 [5.9%], 95% CI: 0.015 to 0.8, $P=0.015$), tandem cervical internal carotid artery/middle cerebral artery 0.7 (6 of 22 [27%], 95% CI: 0.3 to 1.9, $P=0.5$), and basilar artery 0.96 (3 of 10 [30%], 95% CI: 0.2 to 4, $P=0.9$). Prerecombinant tissue plasminogen activator National Institutes of Health Stroke Scale score, systolic blood pressure, glucose, and Thrombolysis in Brain Ischemia flow grade at the occlusion site were the negative independent predictors for complete recanalization in the final model. There were no associations among time to treatment, stroke mechanisms, or recanalization rate. Patients with no flow (Thrombolysis in Brain Ischemia 0) at the occlusion site had less probability of complete recanalization than patients with dampened flow (Thrombolysis in Brain Ischemia 3) (OR_{adj}: 0.256, 95% CI: 0.11 to 0.595, $P=0.002$). Continuous transcranial Doppler monitoring (exposure to ultrasound) was a positive predictor for complete recanalization (OR_{adj}: 3.02, 95% CI: 1.396 to 6.514, $P=0.005$). National Institutes of Health Stroke Scale score ≤2 at 24 hours was achieved in 66 of 305 patients (22%): distal middle cerebral artery 33% (35 of 107), tandem cervical internal carotid artery/middle cerebral artery 24% (5 of 21), proximal middle cerebral artery 16% (24 of 155), basilar artery 25% (2 of 8), and none of the patients with terminal internal carotid artery had dramatic recovery (0%, n=14; $P=0.003$). Modified Rankin Scale score ≤1 was achieved in 90 of 260 patients (35%): distal middle cerebral artery 52% (50 of 96), proximal middle cerebral artery 25% (33 of 131), tandem cervical internal carotid artery/middle cerebral artery 21% (3 of 14), terminal internal carotid artery 18% (2 of 11), and basilar artery 25% (2 of 8) ($P<0.001$). Patients with distal middle cerebral artery occlusion were twice as likely to have a good long-term outcome as patients with proximal middle cerebral artery (OR: 2.1, 95% CI: 1.1 to 4, $P=0.025$).

Conclusions—Clinical response to thrombolysis is influenced by the site of occlusion. Patients with no detectable residual flow signals as well as those with terminal internal carotid artery occlusions are least likely to respond early or long term. **(*Stroke*. 2007;38:948-954.)**

Key Words: diagnostic methods ■ outcome ■ stroke ■ thrombolysis ■ transcranial Doppler

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Intravenous (IV) tissue plasminogen activator (rt-PA) remains the only treatment approved in North America for acute ischemic stroke with the number needed to treat of 8 to reverse one stroke completely at 3 months.[1] However, half of rt-PA-treated patients remain severely disabled or die within this period of time. Several factors predict stroke outcome, including initial stroke severity, older age, high blood pressure, coronary heart disease, and hyperglycemia on admission.[2–5] In patients treated with IV rt-PA, stroke severity, systolic hypertension, early ischemic changes on CT, persistent arterial occlusion, and time to thrombolytic treatment were repeatedly demonstrated as independent predictors of poor outcome.[6–12]

Little is known about whether patients treated with IV rt-PA have different short- and long-term outcomes dependent on the site of occlusion. Previous angiographic studies with intraarterial thrombolysis suggest more proximal occlusions carry greater thrombus burden and are less likely to benefit from local therapy.[13,14] Transcranial Doppler (TCD) is a noninvasive method of occlusion localization and continuous monitoring well suited for thrombolysis.[15] We have previously described and validated the residual blood flow signals classification that can be used for detection and localization of intracranial and tandem occlusions.[16–18] Our goal was to evaluate if the site of arterial occlusion influences the rate of complete recanalization and subsequent clinical outcomes among patients with acute ischemic stroke who receive IV rt-PA treatment.

Subjects and Methods

This was a retrospective study of consecutive patients presenting with acute stroke eligible for systemic thrombolysis at 4 stroke centers (University of Texas–Houston, Universitat Autònoma de Barcelona, University of Calgary, and University of Alberta) from 2000 to 2003. Patients received standard IV rt-PA therapy (0.9-mg/kg dose, maximum 90 mg, 10% bolus, 90% continuous infusion) within the first 3 hours after symptom onset according to the National Institute of Neurological Disorders and Stroke protocol.[1] Patients enrolled in clinical trials of ultrasound-enhanced IV rt-PA thrombolysis were included in this analysis as well as those treated after 3 hours at similar or lower rt-PA doses, ie, 0.6 mg/kg (maximum 60 mg) using ethics committee-approved protocols.

Before IV rt-PA bolus, an experienced sonographer (registered vascular technologist, American Society of Neuroimaging certification in Neurosonology, or MD who is a registered vascular technologist or American Society of Neuroimaging-eligible with TCD practice track over 1 year) identified residual flow signals at the presumed thrombus location using the Thrombolysis in Brain Ischemia (TIBI) flow-grading system.[16] The flow signals are graded on a 0 to 5 scale: grade 0=absence of residual flow signals in the artery of interest through a ultrasound window showing flow in other arteries, grade 1=minimal flow with systolic spikes and absent diastolic flow, grade 2=blunted systolic flow acceleration with mean flow velocity greater or <30 cm/sec and positive end diastolic flow, grade 3 = dampened signals with normal systolic acceleration but decreased mean flow velocity >30% compared with the normal side, grade 4=stenotic flow with increased focal flow velocity and low resistance, and grade 5=normal flow signals. Complete recanalization was defined as occurrence of flow grade 4 or 5. This system as well as our TCD criteria specific to an acute occlusion location has >90% accuracy parameters compared with any type of angiography and, combined with carotid duplex, 100% agreement with urgent digital subtraction angiography to detect lesions amenable to intervention.[19] A 2-MHz transducer was positioned at a constant angle of insonation with a standard head frame (Marc series; Spencer Technologies, Seattle, WA). The depth that displayed the worst residual TIBI flow signal was selected. The TCD waveforms were interpreted from the real-time display at bedside by the same sonographer. Treating physicians were informed about recanalization, reocclusion, or persisting occlusion on TCD if this information was deemed clinically necessary. Our criteria for recanalization and reocclusion were also previously validated and all centers were certified in TIBI flow grading before study initiation.[20]

Patients were included in this study if they had proximal arterial occlusion on baseline TCD: M1 occlusion of the middle cerebral artery (MCA) was suspected if abnormal TIBI flow signals were found at a depth of ≥45 mm; M2 MCA at depths <45 mm; terminal internal carotid artery (TICA) at depths 60 to 70 mm; tandem proximal internal carotid artery (ICA)/MCA when abnormal TIBI signals at depths 30 to 65 mm were found with signs of collateralization of flow through anterior, posterior communicating, or ophthalmic arteries; terminal vertebral artery at depths 40 to 75 mm; and basilar artery (depths 75 to 100 mm) according to previously validated criteria.[17,18] The cervical carotid artery status was assessed by carotid duplex ultrasound that was done either in the emergency room at the time of treatment or during the same hospital admission. The Doppler studies were interpreted according to the Strandness criteria and secondary criteria using Moneta's values for the 60% and 70% levels of stenosis criteria.[21,22] Treating physicians decided to treat with IV rt-PA irrespective of ultrasound findings. Patients with no occlusion on TCD or no temporal window were excluded from our study population.

Neurologic status was repeatedly assessed using the National Institutes of Health Stroke Scale (NIHSS) at baseline and during the first 2 hours after rt-PA bolus by the treating neurologist who was not involved in TCD but who was informed about worsening of flow signals on TCD, if these occurred. All neurologists who performed serial neurologic examinations in the emergency room were certified in the NIHSS scoring. The NIHSS scores at 24 hours and modified Rankin scores at 3 months were obtained by a neurologist who was not blind to the TCD findings. In case of clinical worsening within 24 hours after IV rt-PA treatment, a head CT was ordered and NIHSS score was obtained at the

TABLE 1. Clinical Outcomes at 24 Hours and 3 Months and the Recanalization Rates After IV t-PA Treatment

Factors	Proximal MCA	Distal MCA	Tandem ICA/MCA	Terminal ICA	Basilar Artery	*P* Value
No. (%)	166 (51%)	116 (35%)	22 (7%)	17 (5%)	10 (3%)	
Age (mean±SD)	69±14	69±13	64±12	70±14	75±10	0.3‡
Baseline NIHSS median (range)	18 (6–32)	13 (3–29)	19 (6–29)	20 (11–28)	27 (7–35)	<0.001†
Complete recanalization ≤2 hours of rt-PA bolus	49/163 (30%)	50/113 (44%)	6/22 (27%)	1/17 (6%)	3/10 (33%)	0.007*
24 hours NIHSS ≤2; no. (%)	24/155 (15.5%)	35/107 (33%)	5/21 (24%)	0/14 (0%)	2/8 (25%)	0.004*
3 months modified Rankin Scale score ≤1; No. (%)	33/131 (25%)	50/96 (52%)	3/14 (21%)	2/11 (18%)	2/8 (25%)	<0.001*
Mortality at 3 months	31/131 (24%)	16/96 (17%)	2/14 (14%)	5/11 (45%)	6/8 (75%)	0.0024*
Symptomatic intracranial hemorrhage	20/166 (12%)	5/116 (4%)	1/22 (5%)	2/17 (12%)	3/9 (33%)	0.018*

P values have been calculated by *Fisher exact test, †Kruskal-Wallis H test, and ‡analysis of variance.

same time. Symptomatic intracerebral hemorrhage was defined by ≥4 NIHSS point worsening that, in the opinion of the treating physician, was linked to the presence of blood on repeat head CT or MRI scan.

Three outcomes were studied. Complete recanalization is defined by achieving TIBI flow grade 4 or 5 at the occlusion site within 2 hours from the onset of IV rt-PA treatment. Two clinical outcomes were measured. We used NIHSS score ≤2 at 24 hours as the early measure of response to thrombolysis and modified Rankin score ≤1 at 3 months as the measure for long-term outcome based on National Institute of Neurological Disorders and Stroke rt-PA trial data.[23] Comparison was made between each occlusion group and dramatic recovery (NIHSS score ≤2 at 24 hours) and the rate of good outcome at 3 months (modified Rankin score ≤1).

Statistical analysis included descriptive statistics (mean±SD or median with range for continuous and number [percentage] for categorical variables); χ^2 and Fisher exact test were used to compare proportion; and 2-sample Student *t* tests, analysis of variance, and Kruskal-Wallis H test were used to compare continuous response variables between the groups. In addition, multiple logistic regression was carried out to measure the ORs of good long-term outcome after controlling for other risk factors likely affecting outcomes (age, sex, baseline serum glucose, systolic blood pressure, baseline NIHSS, time to rt-PA treatment, and rt-PA dose).

The OR of complete recanalization was calculated based on each occlusion site with the reference being the other types of occlusion. Then, stepwise multiple logistic regressions were used to determine predictors of complete recanalization. The variables were age, gender, pretreatment NIHSS, TIBI flow grade, occlusion site, time to rt-PA bolus treatment, stroke subtype (TOAST trial classification), baseline systolic blood pressure, glucose, and ultrasound exposure. Analysis was carried out using SPSS version 14.00 for windows. Probability value <0.05 was considered statistically significant. All probability values were 2-sided.

Results

A total of 335 patients presented with acute stroke and received IV t-PA with TCD examination at 4 stroke centers. The mean age was 69±13 years and 172 (51.5%) were men. Median pretreatment NIHSS score was 16 points (range, 3 to 32 points). The mean time to TCD examination was 140±84 minutes, and mean time to IV rt-PA bolus was 145±68 minutes after symptom onset. Three hundred seven patients received IV rt-PA in less than 3 hours (307 [91.6%]), 22 patients received IV rt-PA in 3 to 6 hours (6.6%), and 6 patients (1.8%) received IV t-PA more than 6 hours after symptom onset. Two hundred seventy-seven patients had continuous TCD monitoring (ultrasound exposure) during IV rt-PA thrombolysis and 58 patients had just intermittent TCD monitoring.

Before or at the time of treatment, bedside TCD showed the presence of a proximal (M1) MCA occlusion in 166 patients (51%), distal (M2) MCA occlusion in 116 (35%), tandem proximal ICA/MCA occlusions in 22 (7%), TICA in 17 (5%), vertebrobasilar occlusions in 13 (3.8%; basilar 10, vertebral 3), and anterior cerebral artery occlusion in one patient (0.2%) (Table 1). Patients with vertebral artery (n=3) or anterior cerebral artery (n=1) occlusions were excluded from the analysis as a result of the small numbers.

Three hundred twenty-five patients had diagnostic TCD immediately after IV rt-PA treatment. After up to 2 hours of monitoring, 109 patients (33.5%) had complete recanalization, 80 patients (24.6%) had partial recanalization, and 136 patients (41.9%) had persistent occlusion.

Based on the occlusion site, distal MCA M2 occlusion had an OR of 2 for complete recanalization (50 of 113 [44.2%], 95% CI: 1.1 to 3.1, P=0.005). Whereas the odds for proximal MCA M1 occlusion was 0.7 (49 of 163 [30%], 95% CI: 0.4 to 1.1, P=0.13), terminal ICA occlusion was 0.1 (one of 17 [5.9%], 95% CI: 0.015 to 0.8, P=0.015), tandem ICA/MCA occlusion was 0.7 (6 of 22 [27%], 95% CI: 0.3 to 1.9, P=0.5), and basilar artery occlusion was 0.96 (3 of 10 [33%], 95% CI: 0.2 to 4, P=0.9) (Tables 1 and 2).

Patients with no detectable flow (TIBI 0) at the occlusion site were less likely to recanalize completely with IV rt-PA treatment than patients with dampened flow (TIBI 3) (OR_{adj}: 0.256, 95% CI: 0.11 to 0.595, P=0.002). Fifteen of 81 patients (18.5%) with TIBI 0 at the occlusion site had complete recanalization, whereas 32 of 69 patients (46%) with TIBI 3 had complete recanalization with IV rt-PA

TABLE 2. Univariate Statistics Between Patients With Complete Recanalization and Patients With Persistent Occlusion

Factors	Patient With Complete Recanalization (n=109, 33.5%)	Patient With Persistent Occlusion (n=216, 66.5%)	*P* Value
Age, y	66.9±14	69.9±13	0.097
Gender			
Male	59 (35%)	110 (65%)	
Female	50 (32%)	106 (68%)	0.6
Baseline NIHSS	14.6±6	17.1±6	<0.001
Time to rt-PA treatment, min	143±52	146±75	0.64
Systolic blood pressure, mm Hg	152±23	159±22	0.01
Glucose, mg/dL	135±51	155±79	0.023
Ultrasound exposure			
Yes	97 (36%)	175 (64%)	0.07
No	12 (23%)	41 (77%)	
TOAST classification			
Cardioembolic	56 (35%)	102 (65%)	
Large-vessel atherosclerosis	26 (35%)	48 (65%)	
Other (eg, dissection)	4 (44%)	5 (56%)	0.7
Unknown	26 (29.5%)	63 (70.5%)	
Type of occlusion			
MCA M1	49 (30%)	114 (70%)	
MCA M2	50 (44%)	63 (56%)	
TICA	1 (6%)	16 (94%)	
Tandem ICA/MCA	6 (27%)	16 (73%)	0.011
Basilar artery	3 (30%)	7 (70%)	
TIBI flow grade			
TIBI 0	15 (18.5%)	66 (81.5%)	
TIBI 1	34 (33%)	70 (67%)	0.002
TIBI 2	28 (39%)	43 (61%)	
TIBI 3	32 (46%)	37 (54%)	
rt-PA dose:			
0.6 mg/kg	6 (33%)	11 (67%)	0.88
0.9 mg/kg	103 (34%)	205 (66%)	

TABLE 3. Final Stepwise Logistic Regression Modeling for Patients Who Had Complete Arterial Recanalization as the Dependent Variable

Factor	Adjusted OR	95% CI for Adjusted OR	*P* Value
TIBI flow grade*			0.009
TIBI 3	1	...	...
TIBI 0	0.256	0.11–0.595	0.002
TIBI 1	0.586	0.28–1.2	0.149
TIBI 2	0.825	0.379–1.79	0.628
Baseline NIHSS	0.94	0.89–0.99	0.019
Age†	0.99	0.97–1.009	0.298
Systolic blood pressure	0.99	0.97–0.998	0.019
Glucose	0.996	0.99–1.0	0.027
Ultrasound exposure	3.02	1.396–6.514	0.005

*TIBI flow grade: TIBI 0, no flow at the occlusion site; TIBI 1, minimum flow; TIBI 2, blunted flow; TIBI 3, dampened flow.

†Age was kept in the model because it is an important biological marker.

treatment. Those who recanalized completely had mean NIHSS score of 14.6±6, mean systolic blood pressure of 152±23 mm Hg, and mean glucose of 135±51, whereas those with persisting occlusion or partial recanalization had mean NIHSS score of 17.1±6, mean systolic blood pressure of 159±22 mm Hg, and mean glucose of 155±79 (Table 2).

When the stepwise logistic regression model was performed with complete recanalization as the dependent variable, pre rtPA NIHSS score, baseline systolic blood pressure, glucose, and TIBI flow grade at the occlusion site were the negative independent predictors for complete recanalization in the final model (Table 3). Continuous TCD monitoring (exposure to ultrasound) was the positive predictor for complete recanalization. Patients who had continuous ultrasound exposure with continuous TCD monitoring during treatment were 3 times more likely to have complete recanalization than patients who had just diagnostic TCD (OR_{adj}: 3.02, 95% CI: 1.396 to 6.514, P=0.005).

Among patients who had subsequent clinical information (305 of 335 [91%]), the early dramatic recovery after IV thrombolysis (NIHSS ≤2 at 24 hours) was achieved in 66 patients (22%) (Table 4). The rate of early dramatic recovery by occlusion site was 33% (35 of 107) for distal MCA occlusion, 24% (5 of 21) with tandem ICA/MCA occlusion, 15.5% (24 of 155) with proximal MCA occlusion, 25% (2 of 8) with basilar occlusion, and none among the patients with TICA occlusions (0 of 14) (P=0.004; Tables 1 and 4). There was a strong correlation between recanalization rate and early clinical recovery (NIHSS score ≤2; P<0.001).

Thirty-one patients had symptomatic intracerebral hemorrhage (9.2%) and 60 patients died within 3 months of their stroke (23%). The symptomatic intracerebral hemorrhage and mortality rate based on occlusion site are summarized in Table 1.

Favorable outcomes (modified Rankin score ≤1 at 3 months) were achieved in 35%, or 90 of 260 patients available for follow up (follow up completed in 260 of 335 patients [78%]). Based on the occlusion site, favorable

TABLE 4. Univariate Statistics Between Patients With Good Short-Term Outcome (NIHSS ≤2) and Those With Poor Outcome

Factors	Patient With Good Short-Term Outcome (n=66, 22%)	Patient With Poor Outcome (n=239, 78%)	*P* Value
Age, y	68±13	69±14	0.6
Gender			
Male	37 (24%)	119 (78%)	
Female	29 (20%)	120 (80%)	0.4
Baseline NIHSS	13±5	17±6	<0.001
Time to rt-PA treatment, min	133±37	147±72	0.11
Systolic blood pressure, mm Hg	156.5±20	156.7±22	0.93
Glucose, mg/dL	138±55	152±76	0.17
Ultrasound exposure			
Yes	55 (22%)	192 (78%)	0.63
No	11 (19%)	47 (81%)	
TOAST classification			
Cardioembolic	27 (18%)	120 (82%)	
Large-vessel atherosclerosis	16 (24%)	51 (76%)	
Other (eg, dissection)	1 (12.5%)	7 (87.5%)	0.44
Unknown	22 (26.5%)	61 (73.5%)	
Type of occlusion			
MCA M1	24 (15.5%)	131 (84.5%)	
MCA M2	35 (33%)	72 (67%)	
T ICA	0 (0%)	14 (100%)	
Tandem ICA/MCA	5 (24%)	16 (76%)	0.004
Basilar artery	2 (25%)	6 (75%)	
TIBI flow grade			
TIBI 0	11 (14.5%)	65 (85.5%)	
TIBI 1	20 (21%)	77 (79%)	0.16
TIBI 2	15 (23%)	50 (77%)	
TIBI 3	20 (30%)	47 (70%)	
rt-PA dose			
0.6 mg/kg	2 (15%)	11 (85%)	
0.9 mg/kg	64 (22%)	228 (78%)	0.6

outcomes were achieved by 52% of patients with distal MCA occlusions (50 of 96), proximal MCA occlusions 25% (33 of 131), tandem ICA/MCA occlusions 21.4% (3 of 14), TICA occlusions 18% (2 of 11), and basilar occlusions 25% (2 of 8) (P<0.001; Tables 1 and 5).

After adjusting for age, sex, baseline glucose, systolic blood pressure, baseline NIHSS, time to rt-PA treatment, and rt-PA dose, patients with distal MCA occlusion were twice as likely to achieve favorable outcomes than patients with proximal MCA occlusion (OR: 2.1, 95% CI: 1.1 to 4, P=0.025). Patients with distal MCA occlusions showed a trend toward being 3 times more likely to achieve favorable outcomes than patients with TICA occlusions (OR: 3, 95%

TABLE 5. Univariate Statistics Between Patients With Good Long-Term Outcome (modified Rankin Scale score ≤2) and Those With Poor Outcome

Factors	Patient With Good Long-Term Outcome (n=90, 35%)	Patient With Poor Long-Term Outcome (n=170, 65%)	*P* Value
Age, y	69±12	69±14	0.66
Gender			
Male	49 (37%)	81 (63%)	
Female	41 (31.5%)	89 (68.5%)	0.3
Baseline NIHSS	14±5	17.5±6	<0.001
Time to rt-PA treatment, min	132±34	144±55	0.57
Systolic blood pressure, mm Hg	155±23	158±23	0.3
Glucose, mg/dL	145±80	151±72	0.5
Ultrasound exposure			
Yes	73 (36%)	132 (64%)	0.5
No	17 (31%)	38 (69%)	
TOAST classification			
Cardioembolic	43 (35%)	79 (65%)	
Large-vessel atherosclerosis	18 (30%)	42 (70%)	
Other (eg, dissection)	2 (33%)	4 (67%)	0.8
Unknown	27 (37.5%)	45 (62.5%)	
Type of occlusion			
MCA M1	33 (25%)	98 (75%)	
MCA M2	50 (52%)	46 (48%)	
T ICA	2 (18%)	9 (82%)	
Tandem ICA/MCA	3 (21%)	11 (79%)	<0.001
Basilar artery	2 (25%)	6 (75%)	
TIBI flow grade			
TIBI 0	14 (23%)	46 (77%)	
TIBI 1	25 (31%)	56 (69%)	0.034
TIBI 2	22 (38%)	36 (62%)	
TIBI 3	29 (47.5%)	32 (52.5%)	
rt-PA dose			
0.6 mg/kg	2 (29%)	5 (72%)	0.7
0.9 mg/kg	88 (35%)	165 (65%)	

CI: 0.5 to 15, $P=0.2$; see the Figure for examples of patients with distal MCA and TICA occlusions).

Discussion

Our study showed distal MCA occlusions are more likely to recanalize with IV rt-PA therapy, yet some rate of recanalization can also be expected across all levels of occlusion. Ultrasound exposure by TCD monitoring during IV rt-PA treatment augments the recanalization rate. Our study also showed clinical recovery at both 24 hours and 3 months is influenced by the site of occlusion independently of other factors that can affect outcomes in IV rt-PA-treated patients. Terminal ICA occlusions were the least likely to recanalize or have clinical recovery with IV rt-PA compared with other occlusion locations.

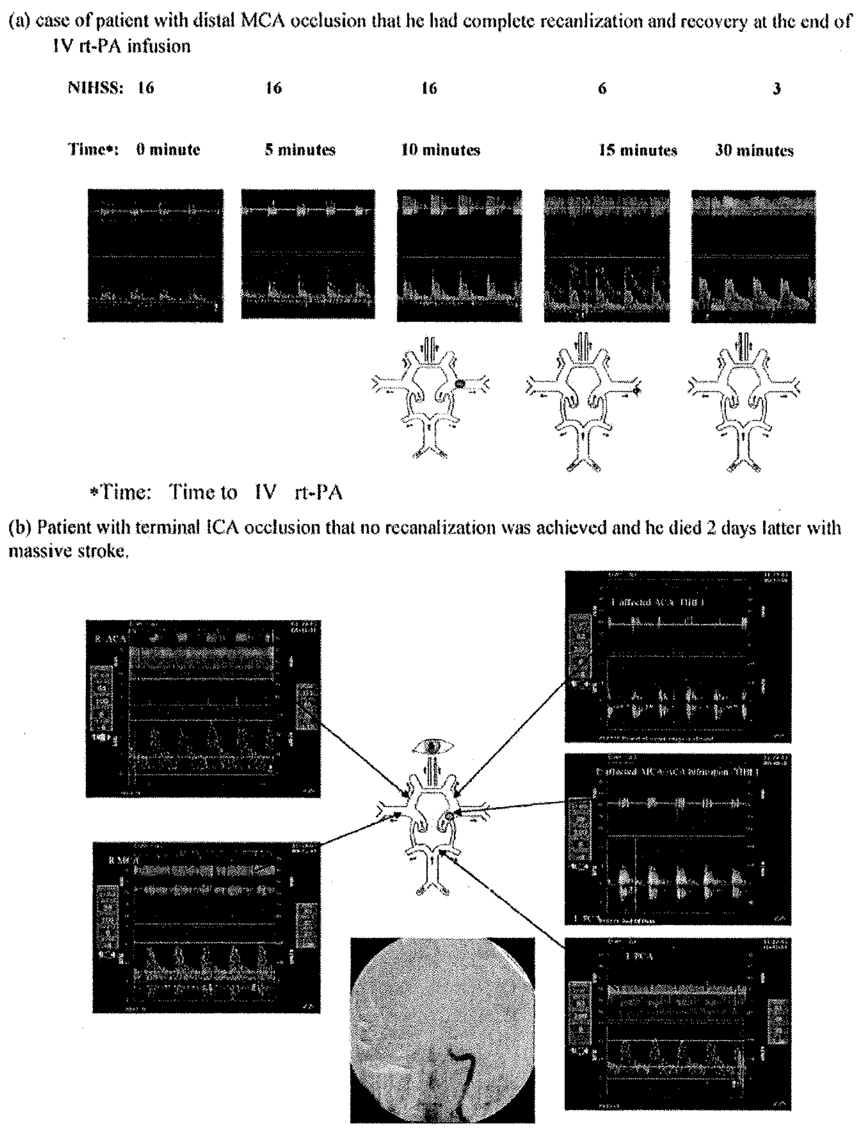
A significant proportion of patients with any occlusion site, including the basilar artery and tandem cervical ICA/MCA lesions, achieved favorable outcomes with IV rt-PA alone. The overall rate of favorable outcome of 35% is similar to NINDS rt-PA Stroke Study[1] and phase IV multicenter trials of IV rt-PA.[6,24] This supports the role of intravenous rt-PA as front-line treatment that can be rapidly initiated. Recanalization induced by rt-PA can be further amplified with diagnostic ultrasound and nanobubbles, and this approach is currently studied in multicenter trials.[25,26] Patients with persisting arterial occlusions may further benefit from combined IV/intraarterial therapy that is also under investigation.[27] TCD can be a suitable noninvasive tool for selecting patient with persistent arterial occlusions despite initial IV rt-PA treatment with an IV/intraarterial protocol.[28] Animal models of temporary arterial occlusions have shown that the salvage of penumbral brain tissue is dependent on time to reperfusion (the concept of "time is brain").[29] Unfortunately, we were unable to include the time of recanalization in our analysis because some patients had periodic TCD examinations and the time of recanalization is not accurately determined.

Poor recanalization and outcome rates with terminal ICA compared with tandem cervical ICA/MCA occlusions can be attributable to larger thrombus burden and poor collaterals with terminal ICA occlusions.[30–32] Sonographically, we distinguish these occlusions by identifying TIBI flow grades 4 and 5 at 60- to 70-mm depths that imply patency of the terminal ICA segment in the presence of a proximal ICA lesion. This, in turn, indicates better collateral supply and fragmented thrombus burden compared with terminal ICA occlusion when markedly diminished or absent residual flow is found over ICA bifurcation (TIBI grades 0 to 3). This hypothesis needs to be tested in a larger sample including assessment of collaterals with angiography.

We did not find an association between the onset to IV rt-PA treatment and recanalization rate. These findings might be explained by the presence of more than one factor in defining the maturation of the clot and the recanalization rate, for example, baseline NIHSS measuring stroke severity, patient age, the density of the clot measured by the TIBI grade, and systemic factors (systolic blood pressure and glucose).

As demonstrated previously, the degree of residual flow signals determines the likelihood of recanalization.[33] For example, patients with detectable residual flow signals (TIBI 1 to 3) are twice as likely to recanalize with any occlusion location compared with TIBI 0 grade. Also, early flow improvement on TCD within the first 30 minutes after rt-PA bolus predicts a greater chance of early recanalization and better short-term recovery from stroke.[34] All these additional factors indicate monitoring of the early recanalization process may help select patients who will sustain benefit from IV rt-PA alone and those who do not respond and may require transfer to comprehensive stroke centers for additional rescue procedures.

Our results parallel findings by del Zoppo et al who studied the effect of IV rt-PA in less than 8 hours from symptom onset using digital subtraction angiography. Digital subtraction angiography demonstrated patients with proximal ICA occlusions had less chance for recanalization than patients with distal MCA occlusion.[35] Also, the Interventional Man-



Examples of patients with distal MCA occlusion and terminal ICA occlusion. a, A patient with distal MCA occlusion who had complete recanalization and recovery at the end of IV rt-PA infusion. b, A patient with terminal ICA occlusion who had no recanalization had died 2 days later with a massive stroke.

agement of Stroke bridging trial showed patients with more proximal occlusions are less likely to achieve complete recanalization by the combined therapy than patients with distal occlusion.[13] In parallel with these observations, our study showed patients with distal MCA occlusion are twice as likely to have a better outcome than those with proximal MCA occlusions.

Our study has limitations. First, an unknown number of patients were excluded from this study if they did not have demonstrated occlusion on TCD or had inadequate TCD quality (inadequate temporal window). The retrospective nature of the analysis precludes any information on patients that the TCD operator failed to find. Outcomes of these patients are not known. Second, TCD is an operator-dependent tool and bias in the interpretation cannot be excluded. Certification has been used to increase reliability of the TCD technique in a multicenter study. In addition, because TCD examinations were not read centrally, reader bias could not be avoided in this study. Third, our study is a retrospective analysis of prospectively collected data, and it might be prone to the effect of confounders and patient selection bias. In addition, the follow-up rate at 3 months was 78%. Finally, conclusions regarding the occlusions in the ICA and vertebrobasilar system are limited by the small numbers in our cohort study.

In conclusion, early response to thrombolysis is influenced by the site of occlusion as determined by residual flow signals on TCD. Terminal ICA occlusions are least likely to respond early or long term. Ultrasound exposure during IV rt-PA treatment augments the recanalization rate. A significant proportion of patients with any occlusion site, including tandem ICA and MCA occlusion, achieve good outcome with IV rt-PA alone.

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Disclosures

A.V.A. is on a speaker's bureau and has received honoraria from Genentech. A.M.D. is on a speaker's bureau for BMS, Sanofi,

AstraZeneca, and Hoffman-La Roche and is also a consultant for Terumo, BMS, and Sanofi. K.U. is a consultant for Mitsubishi Pharma. All other authors have no disclosures to report.

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Site of Arterial Occlusion Identified by Transcranial Doppler Predicts the Response to Intravenous Thrombolysis for Stroke

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